

CLAIMS

1. Butyric ester of hyaluronic acid wherein the hydroxyl groups of hyaluronic acid are partially esterified with butyric residues characterised by a degree of substitution with butyric residues (ratio of number of butyric acid residues to
5 disaccharide units GlcNAc-GlcUA) of less than or equal to 0.1.
2. Ester as claimed in claim 1 characterised by a degree of substitution comprised from 0.001 to 0.08.
3. Ester as claimed in claim 2 characterised by a degree of substitution comprised from 0.002 to 0.03.
- 10 4. Ester as claimed in claim 2 characterised by a degree of substitution comprised from 0.003 to 0.01.
5. Ester as claimed in claims 1-4 wherein the molecular weight of the hyaluronic acid is between 10,000 and 100,000 D.
6. Ester as claimed in claims 1-4 wherein the molecular weight of the ester is
15 comprised from 50,000 to 85,000 D.
7. Process for preparing hyaluronic acid butyric esters in homogeneous phase under anhydrous conditions, characterised by using hyaluronic acid in the form of a quaternary nitrogen salt.
8. Process as claimed in claim 7 for preparing the butyric esters of hyaluronic acid
20 having a degree of substitution less than or equal to 0.1 comprising the following steps:
 - a) dissolving a quaternary nitrogen salt of hyaluronic acid at a concentration comprised between 1-100 g/litre in a polar aprotic solvent optionally heated to a temperature above 50°C,
 - 25 b) preparing the acylating reagent by mixing butyric anhydride and a 4-dialkylaminopyridine in a polar aprotic solvent,
 - c) adding the acylating reagent to the hyaluronic salt solution under anhydrous conditions,
 - d) purifying the reaction product or alternatively converting the ester obtained into
30 the corresponding sodium salt by means of acidification.
9. Process as claimed in claim 8 wherein the quaternary nitrogen salt is a tetraalkylammonium salt.

10. Process as claimed in claim 8 wherein said tetraalkylammonium salt is a tetrabutylammonium salt.

11. Process as claimed in claim 8 wherein step a) and step b) are carried out in reverse order.

5 12. Process as claimed in claim 8 wherein the polar aprotic solvent in step a) is chosen from DMF and DMSO.

13. Process as claimed in claim 8 wherein in step b) (mixing butyric anhydride and a 4-dialkylaminopyridine) the polar aprotic solvent is DMF and the butyric anhydride and 4-dialkylaminopyridine are mixed in equimolar quantities.

10 14. Process as claimed in claim 13 wherein the 4-dialkylaminopyridine is a 4-dimethylaminopyridine.

15 15. Process as claimed in claim 8 wherein the acylating reagent in step b), comprises butyric anhydride in concentrations comprised from 0.01 to 5 moles/litre or more preferably from 0.1 to 2 moles/litre, is gradually added to the hyaluronic acid salt solution under nitrogen atmosphere, optionally maintaining the resulting solution under mechanical agitation.

16. Process as claimed in claim 15 wherein the acylating reaction is stopped by adding distilled water.

20 17. Process as claimed in claim 8 wherein the purification, see step d) of the process, takes place by converting the quaternary nitrogen carboxylic salt to the sodium salt, then separating the product from the reagents.

18. Process as claimed in claim 17 wherein said separation is achieved by precipitation in acetone, followed by filtration, dialysis of its aqueous solution and lyophilization.

25 19. Process as claimed in claim 17 wherein said conversion is obtained by acidifying the ester obtained with dilute hydrochloric acid and neutralizing with a saturated solution of sodium hydrogen carbonate.

30 20. Process as claimed in claims 7-19 wherein under step c) the acylating reagent is added so as to obtain a molar ratio of butyric anhydride to disaccharide repeating units comprised from 0.004 to 0.3.

21. Process as claimed in claim 20 wherein said molar ratio is comprised from 0.01 to 0.03.

22. Hyaluronic acid butyric esters obtainable by the process as in claims 20-21.

23. Use of the esters as in claims 1-6 and 22 for preparing a medicament for the treatment of pathologies characterised by abnormal cell proliferation.

24. Use as claimed in claim 23 wherein the pathologies characterised by abnormal
5 cell proliferation are primary and metastatic tumours.

25. Use as claimed in claim 24 wherein said tumours are primary and of hepatic origin, or they are hepatic metastases derived from primary tumours localised in other organs.

26. Pharmaceutical composition containing as the active principle a therapeutically
10 effective quantity of at least one butyric ester as claimed in claims 1-6 and 22, optionally in association with other active principles or with other butyric esters, and comprising suitable diluents and pharmaceutically acceptable excipients.

27. Pharmaceutical composition as claimed in claim 26 for oral use, in the form of a granular powder, tablets, pills or gels.

15 28. Pharmaceutical composition as in claim 26 for rectal use, in the form of suppositories or as an enema solution.

29. Pharmaceutical composition as in claim 26 suitable for administration by means of the following routes: systemic, intravenous, intraperitoneal, intraarticular, subcutaneous or intramuscular, in the form of a solution or aqueous suspension.

20 30. Pharmaceutical composition as in claim 26, characterised by comprising at least one other active principle in addition to the hyaluronic acid butyric esters of claims 1-6 and 22.